



The impact of aerobic training intensity on skeletal muscle PGC-1 α , interferon regulatory factor 4, and atherogenic index in obese male Wistar rats

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ABSTRACT

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) is the main regulator in energy metabolism. Training stimulates many processes like mitochondrial biogenesis, glucose metabolism, and fatty acids metabolism. It also increases the capacity of fat oxidation. The purpose of this study was to investigate the effects of eight-week aerobic training of different intensities on PGC-1 α , interferon regulatory factor 4 (IRF4), and atherogenic index in obese male Wistar rats. Twenty-four obese male rats induced by a high-fat diet (weight: 250 to 300 gr, BMI >30g/cm²) were divided into three groups: aerobic training of moderate intensity (MI), aerobic training of high intensity (HI), and the control group (C). The MI and HI training groups carried out exercise training by eight weeks of walking on a treadmill for five sessions/week, 60 min per session, and at a speed of 28 m/min and 34 m/min, respectively. The levels of PGC-1 α in the MI and HI groups significantly increased compared to the C group ($p < 0.05$). Moreover, there was no significant differences between IRF4 levels of MI and HI groups ($p > 0.05$). The serum HDL-C levels increased only in the MI group compared to the C group ($p < 0.05$). The LDL-C, TG, TC, and atherogenic index levels reduced more significantly in MI and HI groups than in the C group ($p < 0.05$). The results show that eight-week aerobic training of two moderate and high intensities may be the signaling pathways to the activation of the PGC-1 α protein (i.e., a key regulator of energy metabolism and mitochondrial biogenesis) in skeletal muscle.

Keywords

Aerobic training, PGC-1 α , IRF4, atherogenic index

Abbreviations

PGC-1 α : Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
IRF4: Interferon regulatory factor 4
FNDC5: Fibronectin type III domain-containing protein 5
AMPK: AMP-activated protein kinase
MI: Moderate intensity aerobic exercise
HI: High-intensity aerobic exercise
C: Control

HDL-C: High lipoprotein lipase-C
LDL-C: Lipoprotein lipase-C
TG: Triglyceride
TC: Total cholesterol
BMI: Body mass index
M \pm SD: Mean \pm Standard Deviation
PPAR- γ : Peroxisome proliferator-activated receptor gamma
UCP1: Uncoupling protein 1

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Introduction

Obesity is one of the most common health problems worldwide [1]. It happens when excess adipose tissue is accumulated in the body [2]. The body contains two types of white and brown adipose tissue that can easily be distinguished through their color. Although white adipose tissue is used to store extra calories in the body, the brown adipose tissue burns adipose tissue in the body and produces heat [3]. In recent studies, researchers have shown that the interferon regulatory factor 4 (IRF4) plays a key role in the process of producing heat in the brown adipose tissue and regulating energy consumption and cold resistance. In this process, some specific hormones, including epinephrine, are activated with a reduction in temperature, and brown adipose tissue produces heat by the activities of a group of genes, collectively referred to as the heat-generating gene expression program. One of the most famous of these genes encodes the uncoupling protein 1 (UCP1) [4, 5].

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is one of the well-known UCP1 encoding genes, the expression of which in the muscular tissue could be effective on UCP1 gene expression and the resultant thermogenesis of brown adipose tissue outside the muscle tissue [6]. The PGC-1α protein is a transcriptional cofactor with a molecular weight of 90 kD with an SR region and a specific RNA adhesion, which can lead to many thermogenesis adaptations [7, 8]. Besides, it is capable of indirect transcriptional stimulation of genes such as UCP1. PGC-1α is a PPAR-γ activating factor that exerts many of its biological effects on energy metabolism [6]. In addition, it has been shown that this factor is expressed as a result of exercise, and it stimulates many processes, such as mitochondrial biogenesis, angiogenesis, alteration of the type of the fiber, and prevention of muscle atrophy [9]. This cofactor is not capable of binding to DNA [5]. According to studies, IRF4 has been identified as a transmitter of the effects of PGC-1α on DNA, which has led to an increase in heat production [5]. Therefore, IRF4 is a key factor in the formation of adipose tissue, the management of fats, and the production of IRF4 with reduced fat intake. On the other hand, animals with adipose tissue lacking IRF4 become obese and are resistant to insulin, and cannot withstand cold [5].

One of the best treatments for obesity is one that simultaneously involves modifying the diet, changing physical activity, and behavioral therapy. The results of the studies have shown that regular exercises could lead to a type of adaptation in antioxidant systems and increased resistance to oxidative stress by increasing the function and the level of PGC1-α & IRF4 and

decreasing excess body fat [5, 10, 11]. In this regard, Suwa et al. investigated the effect of low-intensity aerobic exercise (20 meters per minutes per day for 90 days) and high-intensity (30 meters per minutes, for 60 days); they concluded that after 14 days, in both test groups, the levels of SIRT1 and PGC-1α, hexokinase, mitochondrial proteins, and glucose 4 (GLUT4) are increased in the soleus muscle of male rats [12]. Norheim et al. studied the effects of 12 weeks of combined exercise (aerobic-resistance) each week with four sessions of exercise on 26 inactive men aged 40 to 65 years old. However, before the 12 weeks of exercise, the participants experienced an acute endurance activity for 45 minutes with an intensity equal to 70% of the maximum oxygen consumption. They concluded that there is a significant relationship between the increases of muscle mRNA PGC-1α and FNDC5 mRNA after 12 weeks of exercise. Also, despite the reduction of irisin levels after 12 weeks of exercise, its levels increased after severe activity [13]. Gurd et al. reported that six-week intense periodic exercise could lead to an increase in skeletal muscle enzymes by 36% and in PGC-1α protein by 16% after four days of exercise [14].

Participating in regular physical activities, especially aerobic exercises, relying on muscle glycogen fuels, together with the evacuation of these reservoirs, improves the metabolism of lipids in the body, and by using them, it can increase the energy supply [15]. The beneficial effects of regular exercise in preventing obesity, diabetes, and its complications, and improving health have already been proven [16], but the molecular mechanisms of these beneficial effects remain elusive. The results are not precise about administering the most effective intervention program and their mechanisms for changing the adipose tissue phenotype. Therefore, the purpose of this study is to answer the question that which of the aerobic exercise intensities can stimulate the expression of muscle protein PGC-1α, IRF4, adipose tissue, and atherogenic index in obese male Wistar rats.

Results

At the end of the eight-week aerobic training, the body weight of rats was reduced. Moreover, there was a significant difference between the effects of moderate and high-intensity aerobic exercises on body weight ($p < 0.05$) (Table 1).

According to Table 2, there was no difference between the effects of the eight-week moderate and high aerobic exercise on the concentration of PGC-1α in the muscle tissue of male Wistar rats ($p > 0.05$). Based on the results of *Tukey's* post hoc test, there

was a significant difference between mean concentrations of PGC-1α in muscle tissue of the moderate and high-intensity groups and the control group ($p < 0.05$); while there was no significant difference in IRF4 protein concentration between the moderate and high-intensity groups ($p > 0.05$).

The serum HDL-C level significantly increased in the moderate intensity aerobic exercise group compared to the control group ($p < 0.05$); however, serum HDL-C levels in the high-intensity group increased

compared to the control group, but these changes were not statistically significant ($p > 0.05$). There was a significant difference in mean concentrations of LDL-C ($p < 0.05$), serum TG concentration ($p < 0.05$), serum TC concentration ($p < 0.05$), and atherogenic index ($p < 0.05$) between the moderate and high-intensity groups and the control group. There was no difference between the eight-week moderate and high aerobic exercise on the atherogenic index in obese male Wistar rats.

Table 1.
The variation of PGC-1α, IRF4 proteins, lipid profile, and atherogenic index in the experimental and control groups after eight weeks of aerobic exercise.

Variable	C ^a (Mean ± SD)*	MI ^b (Mean ± SD)*	HI ^c (Mean ± SD)*
PGC-1α (ng/ml)	0.27 ± 0.01	0.31 ± 0.01 [‡]	0.30 ± 0.00 [‡]
IRF4 (ng/l)	41.70 ± 1.85	44.04 ± 4.03	43.35 ± 5.54
HDL-C (mg/dl)	25.37 ± 3.01	28.72 ± 3.37 [‡]	27.58 ± 2.52
LDL-C (mg/dl)	10.42 ± 1.08	9.33 ± 0.98 [‡]	9.24 ± 0.63 [‡]
TG (mg/dl)	68.33 ± 2.16	48.35 ± 9.32 [‡]	48.50 ± 9.73 [‡]
TC (mg/dl)	85.62 ± 8.35	74.11 ± 5.37 [‡]	72.63 ± 9.40 [‡]
Atherogenic index (Unit)	2.41 ± 0.52	1.73 ± 0.32 [‡]	1.68 ± 0.52 [‡]

*: Data are presented as Mean ± Standard Deviation; ‡: The mean difference is significant at 0.05. C^a: control, MI^b: moderate exercise, HI^c: high-intensity aerobic exercise

Table 2.
The content of high-fat and standard food

Contents	Protein	Fat	Carbohydrate	Fiber	Ash	Calcium	Phosphorus	Salt	Humidity	Lysine	Methionine	Methionine + cysteine	Reunin + Tryptophan	Other materials	Kcal energy in grams
High fat (%)	18	39	20	2	1	1	0.7	0.5	5	1.15	0.33	0.63	0.95	10	4.8
Standard (%)	20	3.5	25	14.5	10	1	0.7	0.5	10	1.15	0.33	0.63	0.95	11	3.9

Discussion

The purpose of this study was to compare the effect of eight weeks of aerobic exercise with two different intensities on IRF4 and PGC-1α levels and lipid profile of obese male Wistar rats. Based on the study results, the moderate-intensity aerobic exercise program and high-intensity aerobic exercise resulted in a significant increase in the concentration of PGC-1α

in the muscular tissue of obese male rats compared with the control group. This finding is consistent with the results of Jung et al., Oliveira et al., and Norheim et al. [13, 22-23], but this result is inconsistent with Pekkala et al. [24]. Jung et al. conducted an eight-week ladder-climbing exercise, performed three sessions a week on male rats and found that PGC-1α, AMPK, and mitochondrial biogenesis significantly increased at the end of the period [23].

Oliveira et al. examined the effect of running on a treadmill at speeds of 0.8 to 1.2 km/h, 50 min/day five days a week for eight weeks, on obese male rats. Their results showed that the values SIRT1, AMPK, PGC-1 α , and metabolic enzymes increased significantly [22]. Norheim et al. assessed the effect of one session of acute endurance activity for 45 minutes with an intensity of 70% of maximal oxygen consumption and then 12 weeks of combined exercise (aerobic-resistance), four sessions a week, on 26 inactive men aged 40 to 65 years, and concluded that there was a significant relationship between the increase of muscle mRNA PGC-1 α and FNDC5 mRNA after 12 weeks of combined exercise. Irisin levels decreased after 12 weeks of combined exercise and increased after an acute activity session, and there was no relationship between uncoupling protein 1 mRNA and expression of FNDC5 in subcutaneous adipose tissue or skeletal muscle or plasma irisin levels [13]. On the other hand, Pekkala et al. examined the effects of four types of exercises, one hour of low-intensity aerobic exercise, high-intensity exercise, 21 weeks of long-term aerobic exercise, and a combination of exercises (long-term exercise + resistance exercise) on irisin levels and FNDC5 mRNA expression. They concluded that there was no significant change in PGC-1 α , FNDC5 skeletal muscle, and serum irisin in low-intensity aerobic exercise groups, 21 weeks of long-term aerobic exercise, and combined exercise [long-term exercise + resistance exercise] [24].

The difference in findings may be attributed to different subjects in research that were diabetic or obese. These differences can also be related to the different exercise protocols, including volume and the intensity and different types of exercise programs, measurement methods of the indicators, or differences in the level of plasma or serum levels. The PGC-1 α protein encoded by the PPARGC1A gene is a transcriptional activator and acts as an activator of PPAR γ , and regulates the expression of the UCP1 gene and thermogenesis in the brown adipose tissue. Also, in some cases, it was observed that this protein controlled mitochondrial biogenesis and oxidative metabolism in many cells. This protein can cause mitochondrial biogenesis, angiogenesis, and changes in the type of muscle fibers in the skeletal muscle. It also has resistance to dystrophy and muscle atrophy [25].

It acts as a mediator in many of the biological mechanisms involved in energy metabolism. PGC-1 α was named upon identifying its role in PPAR γ activation. Studies have reported an increase in the gene expression of this protein in a cold environment. This activator controls the mitochondrial biogenesis and respiration by the UCP1 proteins and the respiratory factors of the nucleus [26]. Although this protein

is essential for the thermogenetic reaction of brown adipose tissue, it does not affect the browning process, and in various experiments that increased PGC-1 α expression in the subcutaneous tissue resulted in a change in the phenotype of the adipose tissue in brown adipose tissue; this change was associated with increasing the expression of the UCP1 gene, the respiratory chain proteins, and the oxidative enzymes of fatty acids [27]. In rats whose body fat is resistant to PGC-1 α , the expression of mitochondrial genes and exothermic in the subcutaneous fat is slower. However, in rats lacking the PGC-1 α gene, the expression of biogenic mitochondrial genes in white adipose tissue was not dependent on PGC-1 α . However, its presence was indispensable for inducing the expression of UCP1 and other brown adipose-specific genes. This protein may also be involved in controlling blood pressure, regulating cellular cholesterol homeostasis, and developing obesity [28]. Despite the important roles that have been reported for PGC-1 α in the browning process, data on PGC-1 β is still not widely available, and researchers do not consider a significant role for that. The mechanisms by which PGC-1 α activates the expression of the gene is not well known. Besides, C-terminals include the SR motif and the RNA binding area. This area needs to stimulate the expression of specific endogenous genes and interact with the proteins involved in the processing of RNA and the transport protein particle (TRAPP) complex involved in the initiation of transcription [29]. Moreover, PGC-1 α is related to two other transcriptional complexes with acetyl transfer activity, including GCN5 and TIP60. GCN5 directly acetylated the PGC-1 α in the lysine residue, thereby reducing the PGC-1 α transcription activity. In contrast, SIRT1 increases the function of this cofactor by distilling the PGC-1 α . By SIRT1 activation through activating PGC-1 α , mitochondrial biogenesis, free radical production, and oxidation of fatty acids are controlled [30]. It is believed that two factors of nutritional and hormonal messages affect the levels of PGC-1 α [31]. Researchers believe that reducing glucose and increasing glucagon, catecholamine, and glucocorticoid hormones triggers SIRT1 activation and PGC-1 α deacetylation and increases the oxidation of mitochondrial fatty acids by activating PPAR [32]. Regular long-term exercises seem to positively regulate SIRT1 and PGC-1 α indices [33-34].

According to the study results, the HDL-C serum levels in the moderate-intensity aerobic exercise group were significantly higher than the control group, while serum HDL-C levels in the high-intensity group increased compared to the control group, but these changes were not statistically significant. Differences in the mean concentrations of LDL-C,

TG, TC serum, and atherogenic index were significantly different between the two moderate intensity exercise groups and the high-intensity exercise group compared to the control group. These findings are consistent with the results of Adrien et al. [35], but this result is inconsistent with the findings of Freitas et al. and Romero et al. [36-37]. Adrien et al. found that the concentration of low-density lipoprotein, triglyceride, and total cholesterol serum decreased significantly at the end of the training period by examining the effect of eight weeks of aerobic exercise four sessions a week, along with a diet on lipid profiles [35]. Freitas et al. studied the effects of resistance exercise and aerobic exercise on the lipid profile of inactive young men; they concluded that 14-week exercise in the resistance group only led to a significant decrease in total cholesterol, and it has a significant effect only on triglyceride levels in the aerobic exercise group; it did not lead to significant changes in other variables [36]. Romero et al. reported that 24 weeks of aerobic exercise on treadmill resulted in no significant changes in the serum level of high density lipoprotein [37].

Given the nature of the intervention in this study, which is aerobic, it can be stated that this type of exercise can play a significant role in reducing the level of fatty acids. However, the interference of different variables, such as different laboratory methods, for estimating the results, exercise type, the number of sessions, the duration of the exercise session, and the intensity of exercise, can be other reasons for the difference in our research results [38-39]. But there is still debate about whether the intensity or duration of exercise is effective in reducing body fat [40]. It has been reported that intense exercise reduces appetite and increases resting metabolism, ultimately leading to an increase in the negative energy balance [39]. Therefore, by controlling the volume of exercise, we can examine the effect of exercise intensity, which is another aspect of exercise. But in a low-intensity exercise causes a more considerable decrease in body fat compared to high-intensity exercise. It has been shown that lipolytic activity is heterogeneous in various fat stores [subcutaneous or intra-abdominal]. Intraperitoneal adipose tissue is the most active site for lipolytic activity [41]. Despite the high rate of lipolytic activity of the intra-abdominal fat, it is unlikely to have an important role in providing fatty acids for muscle oxidation during exercise. Therefore, most fatty acids entering the bloodstream are extracted from subcutaneous adipose tissue [42].

During moderate aerobic exercise, approximately half of the needed fatty acids are supplied by subcutaneous adipose tissue, where the fatty acid share of trunk and upper limbs adipose tissue is greater than the lower limbs [43]. The relative share of plasma

fatty acid and intracellular triglycerides to the total amount of fat oxidation during exercise with varying intensity has been studied more in athletic individuals than those non-athletic. During moderate-intensity exercise, most of the oxidized fatty acids result from plasma fatty acids, which, with increasing exercise intensity, the relative share of muscular triacylglycerols increases and can account for half of all fat oxidation. The amount of energy consumed during the intensive exercises (more than 70% of maximum oxygen consumption) is relatively high, and the total fatty acid oxidation is suppressed over its levels during the moderate-intensity exercise [44].

In summary, it can be said that eight-week aerobic exercise with two moderate and high levels of intensity by increasing the amount of muscular PGC-1 α protein and improving lipid profile, including high-density lipoprotein increase and a significant decrease in low-density lipoprotein, total cholesterol, triglyceride, and the atherogenic index, can play an important role in changing the phenotype of adipose tissue from white to brown and be effective in preventing obesity and insulin resistance. Therefore, for more accurate results, further research has to be conducted on the effects of exercise on levels of myokine.

Materials & Methods

Animals

The present research was an experimental study on Wistar rats. Twenty-four healthy Wistar male rats (14 weeks, weighing 250 to 300 g, BMI higher than 30 g/cm²) were used. The BMI was determined using the formula: BMI = Body weight (g) /body length² (cm²). The rats were fed with a standard diet (Behparvar Factory, Mashhad, Iran) for a week to adapt to the laboratory conditions. In order to induce obesity, the obese group had a high-fat diet from week 6 for nine weeks; the high-fat diet contained higher calories and fat than the standard food (energy of 4.8 vs. 3.9 kcal/g and fat of 39 vs. 3.5%). All rats were fed this way for 14 weeks and had free access to water and food throughout this study phase (Table 3). At the end of week 14, the approximate weight of rats reached 250 to 300 grams. All rats had free access to water and food. Animals were randomly divided into three groups: 1) moderate aerobic exercise (n = 8), 2) high-intensity aerobic exercise (n = 8), and the control group (n = 8). It should be noted that the principles of the Helsinki Declaration and the opinions of the Ethics Committee were respected in all research phases. The ethics approval was also obtained from the Ethics Committee for the Research of the Ferdowsi University of Mashhad (Ethic code: IR.MUM. FUM. REC.1396. 131).

Familiarization Stage and exercise protocol

According to Table 4, a moderate and high-intensity aerobic exercise program was designed for eight weeks, five days a week, and one session per day for 60 minutes between 08:00 and noon at different speeds on a rodent treadmill (Mobin Bionic Research Group, Mashhad, Iran; with the ability to adjust the slope of the device from -15 degrees to + 15 degrees, set several successive programs, adjust speed, slope, shock, and acceleration for each individual program). After completing the adaptation level, the

animals (to learn how to adapt to the aerobic exercise protocol) were placed on the treadmill during the first week and walked at a speed of 10 m/min with a zero-degree gradient for 15 minutes. During the second and third weeks, the speed and duration of the training gradually increased so that the average speed rate on the treadmill was 28 m/min, 70-75% of the maximum use of oxygen, and the speed of the high-intensity group on the treadmill was at 34 m/min, equal to 80-85% of the maximal oxygen consumption. In total, the exercise volume in the moderate group was 8.4 km/week, and the high-intensity exercise group was 10.2 km/week [17-19]. After completing the training program, to cool down, the speed of the device was reduced inversely so that the machine's speed reaches zero.

Biopsy and measuring the variables

After 48 hours of the last exercise session and 12 hours fasting, rats of all groups were transferred to the Pharmacology Faculty of the Ferdowsi University of Mashhad. In the first place, the animals were anesthetized in a special sampling space (sterile environment) by a combination of Ketamine (30-50 mg/kg) and Xylazine (3-5 mg/kg). After the confirmation of anesthesia, 5 ml of blood was taken by syringe from the right ventricle of each rat and immediately poured into non-anticoagulant test tubes (20). The adipose and soleus tissue were then quickly removed and transferred to a microtube of 1.5 ml and immediately stored in liquid nitrogen and kept at 80 °C.

The tissue samples were poured into the homogenizer tube

and combined with RIPA buffer solution and then mixed with a homogenizer (Potter Elvehjem, Mashhad, Iran) for 15 seconds. All the steps were taken in an ice container. At the last step, the sample was drawn from the tube by the sampler and poured into a 1.5 ml microtube. The microtube was centrifugated for 20 minutes at a rate of 20,000 RPM at 4 °C. After the completion of the centrifuge, the microtube was removed from the device and supernatants were removed again and transferred to the new microtube, and then the samples were kept in a freezer at -80 °C. The PGC-1α protein level of muscle tissue and IRF4 level of adipose tissue was measured with a rat-specific ELISA kit (EAST-BIOPHARM, Hangzhou, China) with Cat. No. CK-E91412 and Intra-Assay CV of <10%. Serum lipid profile level was measured with Pars Azmoon kits (Tehran, Iran). Equation (1) was used to measure the atherogenic index [21]: Equation (1) = Atherogenic index: High density lipoprotein/ (high density lipoprotein - total cholesterol)

Statistical analysis

The data were analyzed by SPSS 16 at a significant level of *p* < 0.05. After ensuring the normal distribution of the data, using the Shapiro-Wilk statistical test and the homogeneity of variances by Levene's test, one-way analysis of variance (ANOVA) with *Tukey's* post hoc test was used to examine the differences between groups. Furthermore, the criteria for accepting or rejecting hypotheses were considered at the level of *p* < 0.05.

Table 3. Program exercise with moderate and high intensities

weeks	Moderate intensity	High intensity
First	15 min/speed 10 m.min	15 min/speed 10 m.min
Second	27 min/speed 15 m.min	27 min/speed 15 m.min
Third	34 min/speed 20 m.min	35 min/speed 20 m.min
Fourth	40 min/speed 21 m.min	45 min/speed 22 m.min
Fifth	46 min/speed 23 m.min	54 min/speed 24 m.min
Sixth	52 min/speed 24 m.min	59 min/speed 27 m.min
SEVENTH	58 min/speed 26 m.min	60 min/speed 31 m.min
EIGHTH	60 min/speed 28 m.min	60 min/speed 34 m.min

Table 4. The variation of weights in experimental and control groups before and after eight weeks of aerobic exercise.

Variable	Stages	C ^a (Mean ± SD)*	MI ^b (Mean ± SD)*	HI ^c (Mean ± SD)*
Weight (gr)	Pre test	295.75 ± 1.81	295.16 ± 1.40	295.41 ± 2.15
	Post test	302.58 ± 1.16**€	287.41 ± 4.25**€	287.08 ± 4.23**€

*: Data are presented as Mean ± Standard Deviation
‡: The mean difference is significant at 0.05
**: The mean difference is significant in compareison with pre-test values
€: The mean difference is significant in comparison with control group
C ^a: control, MI ^b: moderate exercise, HI ^c: high-intensity aerobic exercise

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Authors' Contributions

KH: Conception of the study, designed research, conducted research, analyzed data, edited the final version of the paper, had responsibility for the final content of the paper. SRAH: Conception of the study, designed research, conducted research, analyzed data, edited the final version of the paper, had responsibility for the final content of the paper. MF: Designed research, data interpretation, edited the final version of the paper. MMZ: Conception of the study, designed research, conducted research, analyzed data, edited the final version of the paper, had responsibility for the final content of the paper.

Competing Interests

The authors declare that they have no competing interests.

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